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<p>(54) Title: PROCESS FOR THE PREPARATION OF AZO- AND/OR DISULFIDE-CONTAINING POLYMERS</p> <p>(57) Abstract</p> <p>Azo- and/or disulfide-containing polymers for use as drug delivery systems having a site specific release of the drug in the colon are obtained by polycondensation or polyaddition of an azo- and/or disulfide containing α,ω-dihydroxy or diamino reagent with a suitable α,ω-difunctional dicarboxylic acid-, diisocyanato-, disulfide-comonomer.</p>		

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PROCESS FOR THE PREPARATION OF AZO- AND /OR DISULFIDE- CONTAINING
POLYMERS.

The present invention relates to a process for the preparation of
azo- and/or disulfide- containing polymers to be used in the
preparation of drug delivery systems providing a site specific
delivery of the active agent in the colon.

5

The novel azo and disulfide containing polymers can be applied
for preparing drug delivery systems that result in a site speci-
fic release of the drug in the lower part of the intestine.

- 10 It has been mentioned in the literature that the colon is a
reductive medium and that enzymes are present which are able to
cleave azo and disulfide bonds in organic molecules.

Peppercorn et al. published in Journal of Pharmacology and
15 Experimental Therapy, 181, 555, 1972 that salicylazosulfapyridine
(a drug applied for the therapeutic treatment of ulcerative
colitis) (azufildine, sulfasalazine) can be cleaved by microflora
in the colon with release of 5-aminosalicylic acid.

- 20 US -patents 4,190,716 and 4,298,595 describe polymers having 5-
aminosalicylic acid linked to a polymer backbone via an aromatic
azo linkage which can be used for the site specific release of
5-aminosalicylic acid in the colon.

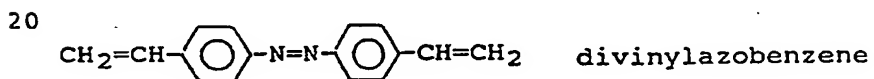
25 US -patent 4,663,308 describes the synthesis of a potentially
crosslinked polymer obtained by radical copolymerization of vinyl
monomers with an azo-containing comonomer which functions as a
crosslinker during polymerization. A typical example of such an

azo-containing crosslinker is 4,4'-divinylazobenzene. The resulting polymers were tested for the preparation of site selective drug delivery systems enabling the release of drug in the colon. Drug delivery systems can consist of systems coated by the azopolymer. The release of the enclosed drug is caused by enzymatic degradation of polymeric coating.

These systems have been proposed as a means to deliver drugs (e.g. peptides) via rectal and oral application to the colon.

10 Preliminary in vivo experiments with vasopressin containing dosage forms, coated with the azo-containing polymers, demonstrated the release of the peptide following oral administration of the novel dosage form. (Saffran, Journal of Pharmaceutical Sciences, 1988; Polymer Preprints, 1988; Science, 1986).

15 The azo-containing polymer systems described by Saffran all have in common their preparation via a copolymerization of vinyl-type monomers with substituted or nonsubstituted divinylazobenzene. This will ultimately lead to crosslinked polymers.



The disadvantage of this procedure is the possibility for cross-linkage of the polymer.

25 The polymers obtained after copolymerization of vinylmonomers with divinylazobenzene are to some extent crosslinked. Crosslinked polymers are insoluble and infusible. The reproducibility of preparing low degree crosslinked and still soluble polymers is anticipated to be very low.

30 The available literature learns that, not only azo bonds but also disulfide bonds can be cleaved in the reductive medium that exists in the lower part of the G.I. tract, i.e. the colon.

35 The reductive potential in caecal contents has been reported in the literature, e.g. by H. Schroder and A. Johansson (Xenobiotica, 3,4, 233-246, 1973). The potentials recorded ranged from -

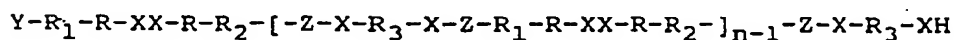
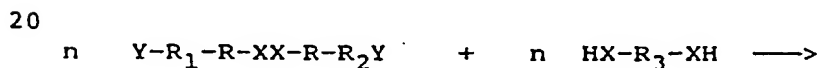
100 to -400 mV. This reductive medium is anticipated to be able to reduce disulfide bonds in organic compounds.

The disulfide bond in glutathione drug conjugates can be reduced in the colon and lead to liberation of the glutathion-linked thiol (G.L. Larsen, J.P. Larson, J.A. Gustafson, Fusobacterium necrophorum, Xenobiotica, 13, 689, 1983).

The objective of the presently described invention is the preparation of a series of azo- and disulfide-containing polymers which are susceptible to reductive cleavage in the gastro intestinal tract, i.e. in the colon, and which will be used for the preparation of colon specific drug delivery systems.

The method by which these reduction cleavable polymers are prepared is the polycondensation or polyaddition of an α, ω -difunctional reagent with an appropriate α, ω -difunctional comonomer.

The reduction sensitive polymers are prepared according to the scheme shown below:



25 with: $-XH = -NH_2, -OH$

$-Y = -COOH, CO-Hal, COOAlkyl, -N=C=O, -CH-CH(R), -SO_2Hal$

$-XX- = -N=N-, -S-S-$

and $R = alkyl, aryl (-\text{C}_6\text{H}_4-)$

30 $R_1, R_2 = alkyl, aryl, alkylaryl$ groups all or not substituted

$R_3 = alkylidene, arylidene, alkylarylidene$ all or not substituted

polyether, polyester

35 $hal = halogen radical, e.g. Cl, Br$

$Z = C=O, NH-C=O, CH_2-CH-OH, SO_2$

and whereby X and Y are interchangeable in the above formulas.

The functional groups in the above reaction equations are selected such that chemical reaction with formation of a covalent bond between the two reagents is feasible, e.g. ester formation, amid formation.

5

In the reaction with component $HX-R_3-XH$ the complementary reagent $Y-R_1-R-XX-R-R_2Y$ can be a diazo compound ($-XX- = -N=N-$) a disulfide compound ($-XX- = -S-S-$) or a mixture of both composed
10 such that the anticipated molarity of the complementary functional groups ($Y-$, resp. $HX-$) is respected.

The molecular weight of the polycondensation or polyaddition polymers generated through the above described reactions can be controlled by proper choice of the molarity of the complementary
15 functional groups as commonly known in polymer synthesis.

The resulting reduction sensitive polymers are in principle linear, not crosslinked, macromolecules, containing an azo and/or a disulfide bond in their polymer backbone.

20



or

25



or

30



This method allows the preparation of a series of azo and/or
35 disulfide containing polymers through a variation in the α, ω -difunctional reagents. So the final physicochemical and physical properties (hydrophilicity, permeability, thermal properties, rheological properties) can be widely varied with the aim of

using these polymers for preparing drug delivery systems. The latter can be matrix type systems or reservoir type systems. In the former case the azo and/or disulfide containing polymer is a major part of the drug containing compartment. In the latter
5 part the azo and/or disulfide containing polymer is used to encapsulate a drug loaded core.

Provided these polymer are stable in the fluids of the mouth, the stomach and the upper intestine the herein described azo and/or
10 disulfide polymers can pass the mouth, stomach and upper intestine without being destructed. In the lower part of the G.I.-tract these reduction sensitive polymers can be cleaved and fragmented by the reductive medium, all or not enzym mediated. The enclosed active agent can be released at the site of
15 degradation.

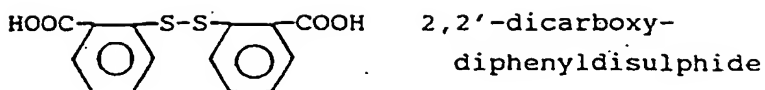
In a first approach to azo-containing polymers azobenzene-4,4'-dicarboxylic acid was used as one constructive part.



For condensation with the appropriate comonomers ($HX-R_3-XH$) the azobenzene-4,4'-dicarboxylic acid was transformed into a reactive derivative, such as a di-acidchloride, a di-paranitrophenolester, di-N-hydroxysuccinimid ester.

25 In one selected type of reaction an α,ω -difunctional azo reagent is reacted with an α,ω -dihydroxy or α,ω -diamino terminated comonomer, oligomer or polymer of the type of a polyether, polyester, polysiloxane, or vinylpolymer.

30 Disulfide containing polymers were prepared in a comparable manner as described above, by reacting 2,2'-dicarboxy diphenyldisulphide with an equimolar amount of an α,ω -dihydroxy or α,ω -diamino terminated comonomer, oligomer or polymer of the type of
35 a polyether, polyester, polysiloxane, or vinylpolymer.



Reduction sensitive polymers containing azo and disulfide bonds
5 were prepared by reacting a mixture of an azo containing diacid and
a disulfide containing diacid with an equimolar amount of an α,ω -
dihydroxy or α,ω -diamino terminated comonomer, oligomer or
polymer of the type of a polyether, polyester, polysiloxane, or
vinylpolymer.

10 Additional characteristics of the present invention will be il-
lustrated in the hereunder described examples and figures.

These figures show:

15 Figure 1.: A matrix device, e.g. a tablet, composed of a
reductive azo and/or disulfide polymer

Figure 2.: A granule coated with a polymer film of the material
described in this invention

20 A first aspect of the present invention comprises the preparation
of polymers containing in their backbone chain azo and/or
disulfide groups. These are prepared by polycondensation or
polyaddition of an α,ω -difunctional azo-containing and/or an α,ω -
25 difunctional disulfide-containing reagent with an appropriate
 α,ω -comonomer.

The second aspect of the present invention comprises the use of
the azo and/or disulfide containing polymers for the preparation
30 of drug delivery systems.

The objective is to design dosage forms, retaining an active
ingredient, which upon oral administration releases the active
agent mainly during passage in the colon. This drug release is
caused by degradation of the polymer, used to design the dosage
35 form, in the reductive medium of the colon. The active agent
being released in the colon can exert a local therapeutic action
in the colon or being absorbed through the intestinal mucosa.

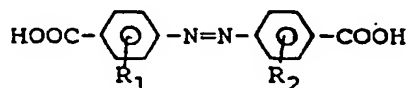
These dosage forms can be of different type:

- a) dosage forms composed of a mixtrure of one or more active agents (drugs), an azo and/or disulfide containing polymer and possible additives
- 5 b) dosage form composed of one or more drugs and one or more additives formulated in a practical form (tablet, granule, capsule). This dosage form is subsequently coated with a film of a reduction sensitive azo- and/or disulfide-containing polymer, all or not mixed with one or more additives. The reduction sen-
- 10 sitive polymers are prepared according to the methods described in this invention.

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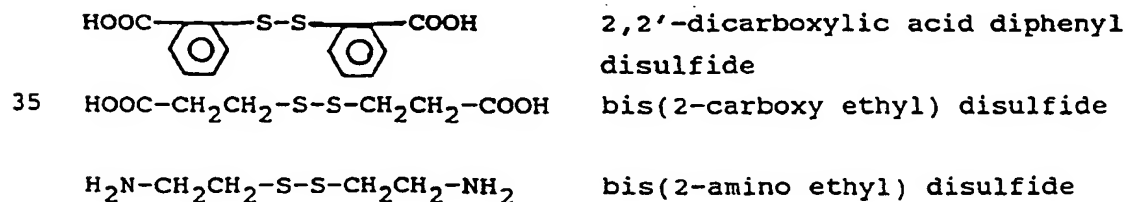
I. DESCRIPTION OF THE STARTING MATERIALS.

One example of an α,ω -difunctional azo compounds used to prepare the azo-containing polymers described in this invention is azo-
 20 benzene-4,4'-dicarboxylic and derivatives thereof :



25 with R_1, R_2 = alkyl, aryl, alkylaryl groups all or not substituted.

Examples of an α,ω -difunctional disulfide used to prepare the disulfide-containing polymers described in this invention are:
 30 2,2'-dicarboxylic acid diphenyl disulfide, bis(2-carboxy ethyl) disulfide, bis(2-amino ethyl) disulfide and derivatives thereof :



X-CO-CH₂CH₂-S-S-CH₂CH₂-CO-X bis(2-haloformyl ethyl)
disulfide (X = Cl, Br,)

bis(2-(succinimidyloxycarbonyl
ethyl) disulfide
(X = succinimidyloxy)

5

First step

10 Preparation of azobenzene-4,4'-dicarboxylic acid.

Azobenzene-4,4'-dicarboxylic acid is prepared starting from 4-nitrobenzoic acid according to the method of Tomlinson (M. Tomlinson, Journal of Chemical society, 756 (1946)).

15 Example 1a

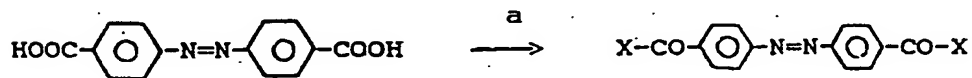
A mixture of 13 g 4-nitrobenzoic acid (0.078 mole) and 50 g NaOH (1.25 mole) in 225 ml of water is heated to 50°C. A solution of 100g glucose (0.56 mole) in 150 ml water is added slowly over 15 minutes at 50°C. Then air is bubbled through the reaction mixture
20 for a period of 48 h. The reaction medium is acidified with acetic acid to pH5. The carboxylic acid is removed by filtration, washed with acetone and ether and dried over phosphorous pentoxide.

25 Second step

Preparation of azobenzene-4,4'-diacid chloride

The azobenzene diacid can be subsequently converted into the diacidchloride, diacidbromide, or a di-reactive ester:

30



with a: a typical reagent well known from basic organic chemistry for this type of conversions.

35 a: SOX₂, SO₂X₂, POX₃, X-CO-CO-X and X = halogen radical, like Cl, Br.

Example 1b

To a solution of 10g (0.074 mole) of azobenzene-4,4'-dicarboxylic acid and 5 ml of DMF in 50 ml toluene is added 45 ml (0.617 mole) SOCl₂. The reaction mixture is refluxed during 8 h. It is then
5 filtered over a G-4 glass filter and allowed to cool down to room temperature. The reaction product separates by crystallization. It is filtered off, recrystallized from isooctane and finally dried. The product is characterized by IR and NMR analysis:
Typical IR adsorptions: -CO-Cl at 1770 cm⁻¹

10 aromatic C-H at 1580, 1540 cm⁻¹
Starting from the azobenzene dicarboxylic acid reactive esters such as 4-nitrophenyl esters, N-hydroxysuccinimide esters and alike can be prepared using conventional methods.

15 Third step

Preparation of bis(2-(succinimidylloxycarbonyl) ethyl) disulfide
The bis-succinimidyl ester of the diacid disulfide can be prepared according to the method of Lomant and Fairbanks (A.J.
20 Lomants, G. Fairbanks, J. Molecular Biology, 104, 243, 1976).

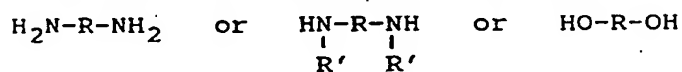
Example 1c

6 g of bis(2-carboxy.ethyl) disulfide is dissolved in 300ml dry dioxane. To this is added 62 mmole N-hydroxysuccinimide and then
25 62,5 mmole N,N'-dicyclohexylcarbodiimide. The mixture is stirred for 24h at room temperature with protection from moisture. The dicyclohexylurea is removed by filtration. The filtrate is then cooled and the dioxane removed by distillation under reduced pressure. The bis(2-succinimidylloxycarbonyl.ethyl) disulfide is
30 purified by repeated recrystallization from acetone/ether. The structure is confirmed by proton NMR.

Fourth step

As complementary α,ω -difunctional reagents to be used as comonomers with an α,ω -difunctional azocompound for the preparation of azo-containing polymers can be used:

a) for the reaction with an α,ω -dicarboxylic acid :
a α,ω -diamine or α,ω -diol of the type:



10 with $\text{R} = (\text{CH}_2)_n$ and n in between 2 and 20
= oligomer, polymer

As α,ω -hydroxy or amino terminated polymers or oligomers can be used polyethers, such as poly(ethylene oxide), poly(propylene oxide), copolymers of ethylene oxide and propylene oxide (random or block copolymers), poly(tetramethylene oxide); polyesters such as polycaprolactone, poly(ethylene terephthalate), poly(butylene terephthalate); polydimethylsiloxane and vinyl polymers e.g. polybutadiene.

b) for the reaction with an α,ω -diamino azo compounds:

An α,ω -dicarboxylic acid of the type $\text{HOOC}-\text{R}-\text{COOH}$

with $\text{R} = (\text{CH}_2)_n$ and n ranging between 2 and 20

25 = polymer or oligomer of the type polyether, polyester, polysiloxane or vinyl polymer as described under pt.a.

The α,ω -dihydroxy and α,ω -diamino reagents can be converted into the α,ω -diisocyanato derivatives by treatment with an appropriate quantity of a diisocyanate, e.g. hexamethylene diisocyanate, toluene diisocyanate, methylenediphenyl diisocyanate, etc...

A series of α,ω -dihydroxy and diamino terminated polymers are commercially available. In addition α,ω -dihydroxy terminated polymers and oligomers can be transformed into the α,ω -diamino terminated polymers by methods well known in organic chemistry.

II. EXAMPLES FOR METHODS TO PREPARE AZO- AND/OR DISULFIDE-CONTAINING POLYMERS

For the preparation of the azo-containing polymer the α, ω -difunctional azo-containing reagent can be replaced partially by another α, ω -difunctional reagent which contains no azo bonds whereby the functional groups are of the same nature as those in the azo-containing reagent. The latter type of α, ω -difunctional reagent may be one containing a disulfide bond.

In an analogous way for the preparation of the disulfide-containing polymer the α, ω -difunctional disulfide-containing reagent can be replaced partially by another α, ω -difunctional reagent which contains no disulfide bonds whereby the functional groups are of the same nature as those in the disulfide-containing reagent. The latter type of α, ω -difunctional reagent may be one containing an azo bond.

As an example in the preparation of an azo-containing polymer starting from azobenzene-4,4'-dicarboxylic acid part of the azo-diacid can be replaced by dicarboxylic acids like oxalic acid, succinic acid, terephthalic acid, bis(2-carboxy ethyl) disulfide, etc...

In the synthesis of these polymers the molecular weight can be controlled by adjusting the molar ratios of the functional groups reacting with one another.

For the preparation of high molecular weight polymers equivalent amounts of the functional groups that react with one another must be used.

The polycondensation or polyaddition reaction can be carried out in solution or in a two phase system.

As an example azo-containing polymer can be prepared by reacting azobenzene-4,4'-diacidchloride with α, ω -diamino poly(tetramethylene oxide) in solution (e.g. in chloroform) and in presence of an acid acceptor like triethylamine.

A number of α,ω -diamino terminated polymers or oligomers are commercially available. They also can be prepared by chemical modification of their α,ω -dihydroxy terminated analogues.

5

Example 2 Preparation of α,ω -amino terminated poly(ethylene oxide) starting from dihydroxy terminated polymer

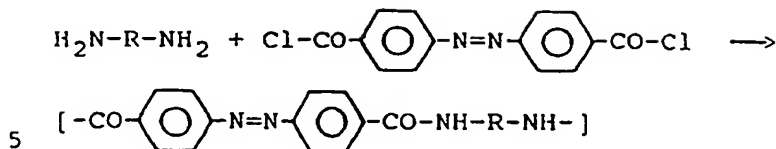
45 g poly(ethylene oxide) is dissolved in 400 ml dry benzene. While stirring under an inert atmosphere 8g butyl lithium is added. Then 35g tosylchloride dissolved in 100 ml of dry benzene is added and the solution is stirred for 12 h at room temperature. The lithium chloride formed during reaction is removed by filtration and the filtrate is concentrated by evaporation. The residue is redissolved in dry ethanol and cooled at -20°C . The ditosylate precipitates and can be isolated by filtration and dried.

5g ditosylate ester of poly(ethylene oxide) is dissolved in 250 ml concentrated ammonia and placed in an autoclave at 120° . The solution is then allowed to cool to room temperature and is concentrated. The residue is dissolved in 20ml 1N sodium carbonate and extracted with toluene. The organic layer is concentrated by evaporation. The residue is dried over phosphorous pentoxide.

25 In a similar manner other α,ω -dihydroxy terminated polymers like poly(tetramethylene oxide), can be converted into the α,ω -diamino terminated derivatives.

Other examples use carboxy-terminated polymers which either are commercially available or can be prepared starting from the α,ω -dihydroxy or diamino terminated polymers using techniques described in the literature.

Example 3a Preparation of an azo-containing polymer by reaction of azobenzene-4,4'-dicarbonylchloride with α,ω -diamino terminated poly(tetramethylene oxide).

Reaction scheme

with $\text{H}_2\text{N}-\text{R}-\text{NH}_2 = \text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{O})_n-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}_2$
 = diamino-pTHF

Experimental part

- 10 The polyamide is prepared by a solution polycondensation. To a solution of 10 g (5 meq) diamino-pTHF (MW 750) dissolved in 100ml chloroform is added 7ml of triethylamine (50 meq). The mixture is stirred for 15 min. at -10°C . Then 3.85 g (25 meq) azobenzene-4,4'-diacidchloride, dissolved in 75 ml chloroform, is added. The
- 15 mixture is stirred for 24h at room temperature, extracted with 0.1N HCl, subsequently 0.1N NaOH. The chloroform layer is dried over magnesium sulfate. The solvent is then stripped off. The reaction product is characterized via IR and NMR analysis.
- IR-adsorptions: $-\text{CO}-\text{NH}-$: $1640, 1540 \text{ cm}^{-1}$; aromatic C-H : 1600
- 20 cm^{-1} . The molecular weight of the polymer as determined by gel permeation chromatography is 26,300.

In a similar manner azopolymers can be prepared by polycondensation of azobenzene-4,4'-dicarbonyl chloride and an

25 α, ω -diamino-terminated poly(ethylene oxide-co-propylene oxide).

The polycondensation can be carried out in solution or in a two phase system (interfacial polymerization).

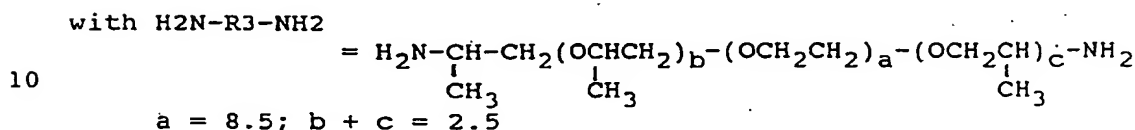
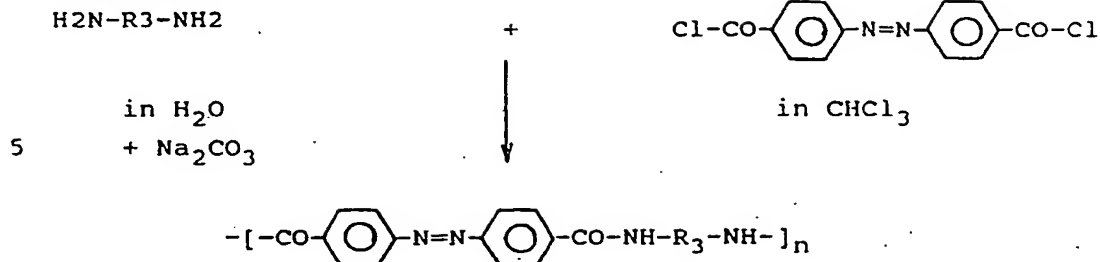
The resulting polymers are essentially linear non-crosslinked

30 macromolecules.

Example 3b

Preparation of an azo-polymer by reaction of azobenzene 4,4'-diacid chloride and α, ω -diamino poly(ethyleneoxide-co-propyleneoxide).

35

Reaction scheme

In this example the polyamide is prepared by an interfacial polycondensation.

15

Experimental

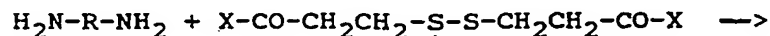
2g (65.15 meq) Jeffamine ED-600 and 1.38g (30 meq) Na_2CO_3 are added to a stirred 250 ml mixture of chloroform/water (1:2, v:v). 10g (65.15 meq) azobenzene-4,4'-diacidchloride dissolved in 125 ml dry chloroform is added. Then the mixture is stirred at room temperature for 6 h. The organic layer is isolated, washed with HCl and NaOH, dried and evaporated. The resulting reaction product is characterized by IR and NMR.

IR absorptions : -CO-NH- 1650, 1535 cm^{-1} , aromatic : 1600 cm^{-1}
 25 Molecular weight (GPC) : 16,400

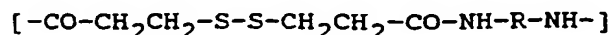
Example 4

Preparation of a disulfide-containing polymer by reaction of bis(2-(succinimidylloxycarbonyl) ethyl) disulfide with an α,ω -diamino poly(tetramethylene oxide) (amino-pTHF).

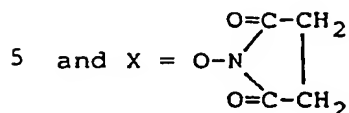
30

Reaction scheme

35



with $\text{H}_2\text{N-R-NH}_2 = \text{H}_2\text{N-CH}_2\text{CH}_2\text{CH}_2\text{O-}(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O-})_n\text{-CH}_2\text{CH}_2\text{CH}_2\text{-NH}_2$
 = diamino-pTHF



Experimental

To a solution of 4.7g (11.95 meq) diamino-pTHF (MW: 750) in 40 ml dry chloroform is added 3.3 ml triethylamine (23.7 meq), and 2.41g (11.95 meq) bis(2-succinimidylloxycarbonyl ethyl) disulfide. The reaction mixture is stirred for 24h at room temperature. The chloroform layer is then extracted with 0.1N HCl and phosphate buffer pH7, resp. the organic layer is dried over MgSO_4 and concentrated under reduced pressure. The structure of the polymer is confirmed by IR and NMR.

In a similar experiment as described in the examples 3b and 4 polymers containing azo and disulfide groups have been prepared by condensing a mixture of an α,ω -difunctional azo-containing reagent and an α,ω -difunctional disulfide containing reagent with an appropriate complementary α,ω -difunctional reagent.

25 III. APPLICATIONS OF AZO- AND/OR DISULFIDE- CONTAINING POLYMERS IN DRUG DELIVERY.

1. Matrix systems

Polymers of the type as described in the present invention can be used as matrix component (indicated in figure 1 by the number 1) in the preparation of drug delivery systems. In such dosage forms the active agent is dissolved or dispersed in a matrix partially or completely composed of an azo- and/or disulfide containing polymer.

35 Dosage forms of this type can be obtained by impregnation of a preformed matrix with a solution of one or more active agents.

Example 5

10g azo-containing polymer obtained by reaction of azobenzene-4,4'-dicarbonylchloride and an α,ω -diamino terminated poly(tetramethylene oxide) is mixed with 1g
5 salicylazosulfapyridine. 0.5g of the powdered mixture is placed in a matrix with an internal diameter of 1 cm. Using a heated press, the mixture is compressed for 2 min at 100°C and at 100 kN. After removal from the matrix a homogeneous tablet is obtained.

10 Alternatively the dosage forms can be prepared by compressing a mixture composed of azo- and/or disulfide-containing polymer, one or more drugs, one or more additives in the form of a tablet or pill, or by extrusion of the mixture.

15 Examples of acceptable additives are vegetable or animal oils and fats, anorganic or organic polymers, e.g. poly(ethylene oxide), poly(vinylpyrrolidone), microcrystalline cellulose, starch, hydroxypropyl methylcellulose, magnesium stearate, talc, lactose,
20 silica and other additives.

2. Polymer coated systems

The above azo- and/or disulfide containing polymers (4 in figure 2) described in this invention can be used for the coating of
25 existing dosage forms (2 in figure 2). This coating can occur by applying a solution or a suspension of the azo- or disulfide polymers. Coating can be performed using well known standard techniques (e.g. spraying, dip coating).

The coating film (4) is selected such that after oral
30 administration of the dosage form the polymer film is degraded selectively in the colon, whereby the drug is being released.

Example 6

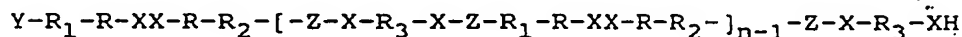
Preparation of hydrogel spheres, loaded with oxprenolol, and
35 coated with an azo-containing polymer.

5g of hydrogel beads (polyHEMA, crosslinked with 0.5 % glycol

dimethacrylate, average diameter 500 μm) are suspended in 50 ml of a 20% (wt) solution of oxprenolol in methylene chloride. After 24h the beads are removed by filtration, washed with one portion of 20 ml chloroform and dried in a rotary evaporator. Extraction experiments and HPLC analysis indicated the drug content being 11%. These drug loaded beads are placed in a miniaturized fluidized bed coater and sprayed with a 10% solution of the azo-containing polymer (example 3) in chloroform. Azo-polymer coated beads are obtained. The average coating thickness can be varied, one example: thickness = 50 μm .

We claim

1. A process for the preparation of azo-containing polymers, disulfide-containing polymers and azo- and
 5 disulfide-containing polymers which can be used for the preparation of drug delivery systems having a site specific release of the drug in the colon, characterized in that they are obtained by polycondensation or polyaddition of an azo- and/or disulfide containing α,ω -difunctional reagent with a
 10 suitable α,ω -difunctional comonomer according to the general reaction scheme illustrated below :



15

with: $-\text{XH} = -\text{NH}_2, -\text{OH}$

$-\text{Y} = -\text{COOH}, \text{CO-Hal}, \text{COOAlkyl}, -\text{N}=\text{C}=\text{O}, -\text{CH}-\text{CH}(\text{R}), -\text{SO}_2\text{Hal}$

$-\text{XX-} = -\text{N}=\text{N-}, -\text{S-S-}$

20

and $\text{R} = \text{alkyl}, \text{aryl} (-\text{C}_6\text{H}_4-)$

$\text{R}_1, \text{R}_2 = \text{alkyl}, \text{aryl}, \text{alkylaryl}$ groups all or not substituted

$\text{R}_3 = \text{alkylidene}, \text{arylidene}, \text{alkylarylidene}$ all or not substituted

25

polyether, polyester

hal = halogen radical, e.g. Cl, Br

with: $-\text{Y} + \text{H-X-} \longrightarrow -\text{Z-X-}$

30 and $\text{Z} = \text{C}=\text{O}, \text{NH}-\text{C}=\text{O}, \text{CH}_2-\text{CH}-\text{OH}, \text{SO}_2$

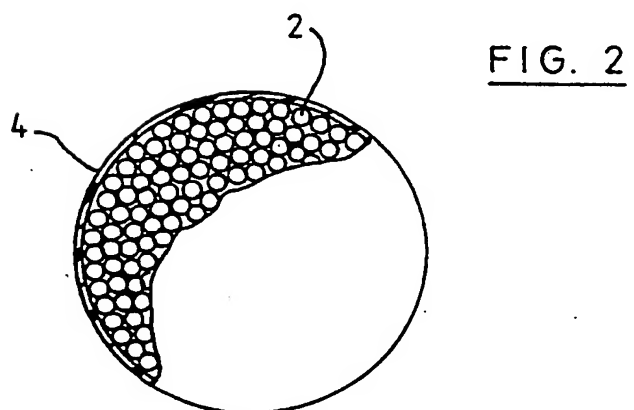
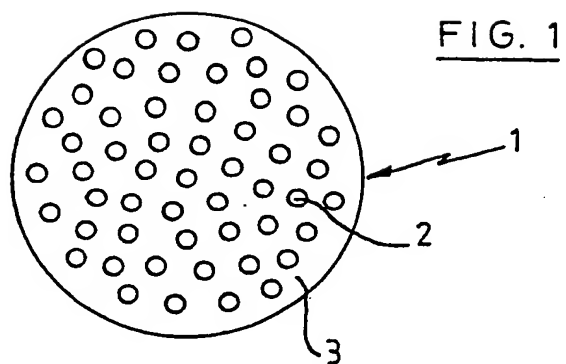
and whereby X and Y are interchangeable in the above formulas.

2. Process of claim 1, wherein as azo-containing α,ω -difunctional
 35 reagent is used azobenzene-4,4'-dicarboxylic acid

3. Process according to claim 1, characterized in that a diacidchloride is prepared such as azobenzene-4,4'-diacidchloride.
- 5 4. Process according to one of the preceding claims characterized in that reactive esters are prepared such as 4-nitrophenyl esters or succinimidyl esters.
5. Process according to one of the preceding claims
10 characterized in that as α,ω -difunctional azo-containing reagent α,ω -diisocyanato derivatives are used.
6. Process according to one of the preceding claims characterized in that reactive disulfide containing esters
15 are prepared such as bis(2-(succinimidyloxycarbonyl) ethyl) disulfide.
7. Process according to one of the preceding claims characterized in that as α,ω -difunctional disulfide-
20 containing reagent bis(2-carboxyethyl) disulfide is used.
8. Process according to one of the preceding claims characterized in that as α,ω -difunctional disulfide-
25 containing reagent bis(2-(chloroformyl)ethyl) disulfide is used.
9. Process according to one of the preceding claims characterized in that as α,ω -difunctional comonomer is used
30 an .. α,ω -dihydroxy- or α,ω -diamino-terminated monomer, oligomer or polymer such as ethers, polyethers, esters, polyesters, siloxane, polysiloxane, alkener, arylene, or alkylarylene, or a vinyl polymer.

10. Process for preparing systems for delivering drugs to the large intestine, comprising a) matrix-type systems wherein the drug is formulated in a matrix containing the said reduction sensitive azo- and/or
5 disulfide containing polymers; b) systems wherein a dosage form is coated one or a mixture of one of the said azo- and/or disulfide containing polymers.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/BE 91/00006

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁸		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁵ : A 61 K 9/22, 9/32, 9/52, C 08 G 69/26, 63/68, 59/28, 18/78, 75/24, 75/30		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification-System	Classification Symbols	
IPC ⁵	A 61 K, C 08 G	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US, A, 4663308 (M. SAFFRAN) 5 May 1987 (cited in the application) -----	
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
27th March 1991		
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	MISS D. S. [Signature]	

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